

New tools for the management of Infectious Diseases

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Introduction

- Few antibiotics have been approved by the FDA during the past decade
- Drug companies performing very few trials for new antibiotics
- No new antibiotic family is expected in the near future
- Emerging resistance to available antibiotics continues to rise, specially in the outpatient setting
 - Community acquired MRSA
 - VRE

Antibiotics

Daptomycin

- **Cubicin**, from Cubist Pharmaceuticals
- Indications:
 - complicated skin and skin structure infections (4mg/kg)
 - *Staphylococcus aureus* bloodstream infections (6mg/kg) including right-sided endocarditis
- Mechanisms of activity – binds to bacterial membranes and causes a rapid depolarization of membrane potential, with inhibition of protein, DNA, and RNA synthesis, resulting in bacterial cell death

Daptomycin

- Cyclic lipopeptide for gram positive bacterial infections (efficacy in vitro and in vivo):
 - *Enterococcus faecalis* (vancomycin-susceptible isolates only)
 - *Staphylococcus aureus* (including methicillin-resistant isolates)
 - *Streptococcus agalactiae*
 - *Streptococcus dysgalactiae* subsp. *Equisimilis*
 - *Streptococcus pyogenes*
 - In vitro efficacy (not confirmed with in vivo trials) include *Corynebacterium jeikeium*, vancomycin resistant *Enterococcus faecalis* and *faecium*, *Staphylococcus epidermidis* (including methicillin resistant) and *Staphylococcus haemolyticus*

Daptomycin dosing

- Dosage adjustment recommended in patients with creatinine clearance < 30 ml/min:
 - 4mg/kg every 48 hours for cSSSI
 - 6mg/kg every 48 hours for bacteremia
 - Administer dose following hemodialysis
- No dosage adjustments needed with mild to moderate hepatic impairment
 - Pharmacodynamics in patients with severe hepatic insufficiency have not been evaluated

Daptomycin – pharmacologic aspects

- Metabolism not clear – not by liver
- Renal excretion is primary route of elimination
- No mechanisms of resistance identified
- *In vitro* synergistic interactions with aminoglycosides, β -lactam antibiotics, and rifampin

Daptomycin – monitoring and precautions

- Development of muscle pain or weakness, particularly of distal extremities
- CPK levels (at least weekly)
- Possibility of developing neuropathy
- Pregnancy category B

Daptomycin Don'ts

- No indications in pediatric population
- Not indicated for treatment of pneumonia
- Not indicated for treatment of left-sided endocarditis

Tigecycline

- **Tygacil**, from Wyeth Pharmaceuticals
- Indicated for treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia
 - 100mg loading dose followed by 50mg IV Q12 hours
- Structurally similar to tetracycline class antibiotics
- Bacteriostatic

Tigecycline

- Activity against gram-positive, gram-negative, and anaerobic organisms
 - *Enterococcus faecalis* (vancomycin susceptible isolates only)
 - *Staphylococcus aureus* (including methicillin-resistant isolates)
 - *Streptococcus agalactiae*
 - *Streptococcus anginosus* grp
 - *Streptococcus pyogenes*
 - *Citrobacter freundii*
 - *Enterobacter cloacae*
 - *Escherichia coli*
 - *Klebsiella oxytoca*
 - *Klebsiella pneumoniae*

Tigecycline

- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Bacteroides vulgatus*
- *Clostridium perfringens*
- *Peptostreptococcus micros*
- In vitro activity against *Acinetobacter baumannii* – no clinical trials available

Tigecycline – pharmacologic aspects

- Glycylcycline that inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome
- No dosage adjustment in patients with renal impairment or hemodialysis
- No dosage adjustment in patients with mild to moderate hepatic impairment
 - Adjustment in maintenance dose in patients with severe hepatic impairment

Tigecycline precautions

- Teratogenic in pregnancy – category D
- May cause permanent discoloration of teeth during tooth development (pregnancy to 8 yrs)
- Administer with caution in patients with history of allergic reaction to tetracyclines
- No indication in pediatric population

Tigecycline adverse events

- Nausea/vomiting – most common
- Photosensitivity
- Pseudotumor cerebri
- Pancreatitis
- Anti-anabolic action – increased BUN, azotemia, acidosis, hypophosphatemia

Gemifloxacin

- **Factive**, from Oscient pharmaceuticals
- Fluoroquinolone
- Oral preparation only – 320mg PO QD
- Indicated for management of acute bacterial exacerbation of chronic bronchitis (5 days) and community acquired pneumonia of mild to moderate severity (7 days)
- Metabolized by the liver
- Fecal and urinary excretion
- No dosage adjustment in presence of hepatic impairment
- Dose adjustment recommended in presence of renal insufficiency – 160 mg QD

Gemifloxacin

- Bactericidal
- Inhibits DNA synthesis through inhibition of both DNA gyrase and topoisomerase IV
- Activity against gram-positive, gram-negative, and other microorganisms:
 - *Streptococcus pneumoniae*
 - *Haemophilus influenzae*
 - *Haemophilus parainfluenzae*
 - *Klebsiella pneumoniae*
 - *Moraxella catarrhalis*
 - *Chlamydia pneumoniae*
 - *Mycoplasma pneumoniae*

Gemifloxacin - precautions

- May prolong QT interval and should be avoided in patients with history of QT prolongation, uncorrected electrolyte disorders (hypokalemia, hypomagnesemia), and patients receiving class IA or class III antiarrhythmic agents (quinidine, procainamide, amiodarone, sotalol)
- May cause tendonitis/tendon rupture (family effect)
- May cause convulsions (family effect)
- May cause rash
- Pregnancy category C
- No pediatric indication

Doripenem

- Doribax, from Ortho-McNeil
- Carbapenem with enhanced activity against some gram-negative bacilli
- Indicated for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis with bacteremia in patients 18 years of age and older
 - 500mg IV Q8 hours
- Pregnancy category B

Doripenem-pharmacologic aspects

- Mechanism of action through penicillin-binding proteins
- Concomitant use of an aminoglycoside may reduce development of resistance in *Pseudomonas aeruginosa*
- Renal adjustments:
 - CrCl 30 to 50 mL/min – 250 mg IV Q 8 hours
 - CrCl less than 30 mL/min but greater than 10 mL/min – 250 mg IV Q 12 hours
 - CrCl less than 10 mL/min – no data

Doripenem

- Active against gram-positive, gram-negative, and anaerobic organisms
 - *E. coli*
 - *Klebsiella pneumoniae*
 - *Pseudomonas aeruginosa*
 - *Bacteroides species*
 - *Streptococcus constellatus* and *intermedius*
 - *Peptostreptococcus micros*
 - *Proteus mirabilis*
 - *Acinetobacter baumannii*
 - *Citrobacter*
 - *Enterobacter*
 - *Serratia*
 - *Clostridium difficile*

Doripenem

- In vitro activity against *Streptococcus pneumoniae*, oxacillin-susceptible *Staph aureus*, oxacillin-susceptible coagulase-negative staphylococci, and *Enterococcus faecalis*
- Not active in vitro against *Enterococcus faecium*
- Active in vitro against extended spectrum beta lactamase producing bacteria

Doripenem precautions

- Contraindicated in patients with known serious hypersensitivity to doripenem or to other drugs in the same class
- Contraindicated in patients who have demonstrated anaphylactic reactions to beta-lactams
- May reduce serum valproic acid levels to subtherapeutic, resulting in loss of seizure control
 - Monitor levels frequently
- No association with increased seizure activity
- Coadministration with probenecid not recommended

Antifungals

Voriconazole

- **Vfend**, by Pfizer Pharmaceuticals
- Triazole antifungal agent
- Indicated for treatment of:
 - invasive aspergillosis,
 - candidemia in nonneutropenic patients
 - disseminated skin, wounds, and intraabdominal infections
 - Esophageal candidiasis
 - Serious infections caused by *Scedosporium apiospermum* and *Fusarium*
- Intravenous and oral preparations
- Interferes with ergosterol biosynthesis
- Oral bioavailability of 96%

Voriconazole

- In vitro activity against *Aspergillus* species, *Candida* species (*albicans*, *glabrata*, *krusei*, *parapsilosis*, *tropicalis*), *Scedosporium apiospermum*, and *Fusarium* species
- In vivo activity against *Candida* species, *Aspergillus*, and *Scedosporium*
- Possible cross-resistance with other azoles

Voriconazole dosing

- Invasive aspergillosis
 - Loading dose of 6 mg/kg Q12 h for the first 24 h, then 4 mg /kg IV Q12 h
 - Oral preparation – 200 mg Q 12 h
- Candidemia in nonneutropenic patients and other deep tissue *Candida* infections
 - Loading dose of 6 mg/kg Q12 h for the first 24 h, then 3-4 mg /kg IV Q12 h
 - Oral preparation – 200 mg Q 12 h
- Esophageal candidiasis – 200 mg PO Q12 h
- Pseudosporiosis and Fusariosis
 - Loading dose of 6 mg/kg Q12 h for the first 24 h, then 4 mg /kg IV Q12 h
 - Oral preparation – 200 mg Q 12 h

Voriconazole - pharmacologic aspects

- Hepatic metabolism
- Renal excretion
- Hepatic impairment – regular loading dose, half maintenance dose
- Avoid intravenous administration in patients with moderate or severe renal impairment
 - Accumulation of intravenous vehicle SBECD
 - Use oral preparation only

Voriconazole drug interactions

- Contraindicated co-administration with rifampin, rifabutin, high-dose ritonavir, efavirenz, carbamazepine and long-acting barbiturates, sirolimus, terfenadine, astemizole, cisapride, pimozide, quinidine, ergot alkaloids
- Caution co-administration with cyclosporine, methadone, tacrolimus, warfarin, statins, calcium channel blockers, sulfonylureas, vinca alkaloids, phenytoin, omeprazole

Voriconazole clinical studies

- In a study for invasive aspergillosis using conventional amphotericin B as comparator, voriconazole demonstrated a higher global satisfactory response and longer patient survival
- A study for candidemia confirmed that voriconazole was comparable to amphotericin B followed by fluconazole

Voriconazole - warnings and precautions

- Visual disturbance - common
 - Blurring
 - Photophobia
 - Color vision change
 - Avoid hazardous tasks, such as driving at night or operating machinery
- Rash – common
- Hepatic toxicity
- Pregnancy category D
- Galactose intolerance
- Avoid strong, direct sunlight

Posaconazole

- **Noxafil**, by Schering Corporation
- Triazole antifungal agent for oral administration (suspension)
- Indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in immunocompromised patients 13 y/o or older and treatment of oropharyngeal candidiasis
- Blocks synthesis of ergosterol
- In vitro activity against *Aspergillus fumigatus* and *Candida albicans*

Posaconazole dosing

- Prophylaxis of invasive fungal infections – 200 mg TID
 - Length of therapy varies based on clinical response
- Oropharyngeal candidiasis – loading dose of 100 mg BID, then 100 mg PO QD
 - 14 days of treatment
- Oropharyngeal candidiasis refractory to itraconazole and/or fluconazole – 400 mg BID
 - Length of therapy varies based on clinical response

Posaconazole - pharmacologic aspects

- Unknown if dose adjustment is needed in hepatic insufficiency – use with caution in patients with hepatic impairment
- No dose adjustment needed in renal impairment
 - Patients with severe renal impairment should be monitored closely for breakthrough fungal infections
- Possible cross-resistance with other azoles
- Administer with food or nutritional supplement to assure adequate absorption
- Fecal/renal excretion

Posaconazole - precautions

- Liver function tests should be evaluated prior to starting therapy and during course of treatment
- Avoid co-administering with drugs known to prolong QT interval – astemizole, cisapride, pimozide, halofantrine, or quinidine
- Avoid co-administering with ergot alkaloids – ergotamine and dihydroergotamine
- Dose reduction of statins recommended
- Dose reduction in calcium channel blockers might be needed
- Pregnancy category C

Posaconazole - clinical studies

- Substantially fewer breakthrough infections by *Aspergillus* species in patients receiving posaconazole prophylaxis when compared to those receiving fluconazole or itraconazole
- Lower clinical failure for patients treated with posaconazole when compared to patients treated with fluconazole and itraconazole

Posaconazole drug interactions

- Cyclosporine and tacrolimus – reduce immunosuppressor dose
- Rifabutin, phenytoin, cimetidine – avoid use

Anidulafungin

- **Eraxis**, by Pfizer Pharmaceuticals
- Echinocandin
 - Inhibits the synthesis of 1,3- β -D-glucan
- Indicated for candidemia, other forms of *Candida* infections (intra-abdominal abscess and peritonitis), and esophageal candidiasis
- In vitro studies demonstrated activity *Candida albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*

Anidulafungin dosing

- Recommended dose:
 - Candidemia or other *Candida* infections – 200 mg loading dose followed by 100 mg QD
 - Esophageal candidiasis – 100 mg loading dose followed by 50 mg QD

Anidulafungin - pharmacologic aspects

- IV preparation only
- No hepatic metabolism (unknown)
- Fecal excretion
- No dose adjustment in hepatic or renal insufficiency, including patients on HD
 - Not dialyzable
- No dose adjustment with immunosuppressors
- Possibility of abnormalities in liver function

Anidulafungin precautions

- Pregnancy category C
- Studies demonstrated significantly more endoscopically-documented relapses of esophageal candidiasis with anidulafungin than with fluconazole
 - Consider suppressive therapy after initial treatment

Micafungin

- **Micamine**, by Roche Pharmaceuticals
- Echinocandin
- Indicated for treatment of esophageal candidiasis and for prophylaxis of *Candida* infections during hematopoietic stem cell transplant
- Only available IV
- Inhibits synthesis of (1,3)- β -D-glucan
- Fecal excretion

Micafungin

- In vitro activity against:

- *C. albicans*
- *C. glabrata*
- *C. parapsilosis*
- *C. tropicalis*
- *C. krusei*
- *C. lusitaniae*
- *C. dubliniensis*
- *Aspergillus* ssp.

Micafungin dosing

- Esophageal candidiasis – 150 mg QD
- Prophylaxis of *Candida* in HSCT – 50 mg QD

Micafungin

- No dose adjustment needed in renal or mild to moderate hepatic impairment
- Has not been studied in patients with severe hepatic dysfunction
- Recommended as an alternative to azole antifungals in patients who have contraindications, adverse events, significant drug interactions, or fluconazole-resistant *Candida* or for those unable to tolerate amphotericin B

Micafungin - clinical studies

- In studies performed for esophageal candidiasis, micafungin demonstrated as good as fluconazole after 14 days of treatment
- In studies performed on prophylaxis of *Candida* in HSCT, overall success was higher in the micafungin group (p=.03)

Consider eliminating from your office if samples still available

- **Telithromycin – Ketek**
 - Serious hepatotoxicity, associated deaths reported in US
- **Gatifloxacin – Tequin**
 - Associated hypoglycemia
 - Not being produced or marketed

References

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